DOI: https://doi.org/10.48305/arya.2024.42018.2915

Vitamin D deficiency and atrial fibrillation: A cross sectional single center study

Amir Askarinejad[1,2], Hooman Bakhshandeh[1], Mona Heidarali[1], Sara Adimi[1], Zahra Ghaemmaghami[1], Majid Haghjoo[2]

Original Article

Abstract

BACKGROUND: Atrial fibrillation (AF) augments the risk of stroke by 4-5 times. Vitamin D is pivotal in numerous metabolic pathways. A handful of studies have explored the correlation between vitamin D deficiency (VDD) and AF outcomes. Hence, the authors sought to assess the relationship between VDD and AF outcomes.

METHODS: From December 2021 to February 2023, 190 patients with AF were incorporated into the authors' study. Given the seasonal fluctuation of vitamin D levels, these levels were examined from the start of December until the end of March.

RESULTS: The final analysis comprised 190 patients (55.8% male) with an average age of 46.22±15.03. Vitamin D deficiency, insufficiency, and sufficiency were noted in 77 (40.5%), 46 (24.2%), and 67 (35.3%) patients, respectively. Fatigue and syncope were significantly more prevalent in the VDD group than in other groups. Three-vessel disease was more frequent in the VDD group (p-value=0.04). Mortality was more prevalent in patients with VDD (6.31%) compared to the VDI (2.10%) and VDS (0.05%) groups (p = 0.03). Successful cardioversion was significantly more prevalent in the VDS group (p = 0.03).

CONCLUSION: A sufficient level of vitamin D was linked with a better response to cardioversion. However, low vitamin D levels are correlated with higher mortality in AF patients.

Keywords: Atrial Fibrillation; Vitamin D; Vitamin D Deficiency

Date of submission: 8/12/2023, ***Date of acceptance:*** 1/29/2024

Introduction

Atrial fibrillation (AF), the most common arrhythmia, impacts 33 million individuals worldwide, with an all-cause mortality rate of 63.3 per 1,000 person-years[1]. The prevalence of AF has escalated in recent years, leading to a surge in mortality and morbidity[2]. Notably, AF amplifies the risk of stroke by 4-5 times[3]. Therefore, it is a significant rhythm disorder with a substantial impact on healthcare systems[4]. Aging, hypertension, valvular heart disease, congestive heart failure, coronary artery disease, and diabetes mellitus are independent risk factors for AF[5]. Despite extensive research on AF, the etiology and underlying pathways remain poorly understood[6]. Vitamin D plays a crucial role in multiple metabolic pathways[7]. Vitamin D is a negative modulator of the renin–angiotensin–aldosterone system (RAAS)[8]. Both RAAS and inflammation play a significant role in the pathogenesis of AF[9,10]. A few studies have investigated the role of vitamin D deficiency (VDD) in the presentation, complications, and mortality of AF. Therefore, the authors aimed to evaluate the association between VDD and AF outcomes.

1- Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran
2- Cardiac Electrophysiology Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran
Address for correspondence: Majid Haghjoo; Cardiac Electrophysiology Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran
Email address: majid.haghjoo@gmail.com

Methods and materials

Study Design and Participants

This cross-sectional study was carried out from December 2021 to February 2023. The protocol was registered and received approval from the authors' local ethics committee (Approval ID: IR.RHC.RHEC.1401.087). All study procedures were performed in compliance with the Declaration of Helsinki. All participants gave written informed consent after the study protocol was explained to them.

All patients diagnosed with AF who were referred to the authors' outpatient department, including the arrhythmia clinic, or were admitted to the hospital, were initially evaluated. Patients with hypo- or hyperthyroidism, chronic renal failure, chronic obstructive pulmonary disorders, malignancy, acute infection, or previous gastrectomy were excluded from the study. Patients who used calcium or vitamin D supplements or any drugs that interfere with calcium metabolism were also excluded from the study. Owing to the seasonal variation of vitamin D, vitamin D levels were measured from the start of December until the end of March. The demographic, clinical, and laboratory data pertaining to the patients who ultimately participated in the study were sourced from the Iranian Registry of Atrial Fibrillation (IRAF)[11].

Definitions

Hypertension

The authors assessed the diagnosis of hypertension using the American Heart Association (AHA) guideline, based on one of these three modalities: office-based, home-based, or ambulatory-based[12]. Additionally, patients with a history of antihypertensive medications were deemed hypertensive.

Dyslipidemia

Dyslipidemia was identified when total cholesterol, low-density lipoproteins (LDL), and triglycerides were equal to or exceeded 240, 160, 200, and 100 mg/dL, respectively, and high-density lipoproteins (HDL) were less than 40 mg/dL[13].

Diabetes

Diabetes was diagnosed according to the 2016 Standards of Medical Care in Diabetes published by the American Diabetes Association (ADA)[14].

Coronary Artery Disease (CAD)

CAD and its severity were diagnosed with coronary angiography or coronary CT angiography in patients who presented with cardiac-related chest pain[15]. Double-vessel disease was defined as the presence of >50% lumen diameter narrowing in two of the three main epicardial vessel systems. Three-vessel disease referred to lumen narrowing of >50% in all three major epicardial artery systems or in the left anterior descending and proximal circumflex in left-dominant coronary arteries[16].

CHA2DS2-VASc Score

The CHA2DS2-VASc Score was computed based on: congestive heart failure (1 point), hypertension (1 point), age ≥ 75 years (2 points), diabetes mellitus (1 point), stroke (2 points), vascular disease (1 point), age 65-74 years (1 point), and female gender (1 point)[17].

AF

AF was diagnosed as irregularly irregular R-R intervals without distinct repeating P waves and irregular atrial activations in a single-lead ECG tracing of ≥ 30 s or the entire 12-lead ECG[18].

Chronic Kidney Disease Diagnosis

Chronic kidney disease was diagnosed if the estimated glomerular filtration rate was less than 60 ml/min/1.73 mt^2 [19].

VDD, Insufficiency (VDI), and Sufficiency (VDS) Definition

VDD, VDI, and VDS were defined as serum 25-hydroxyvitamin D levels of less than 20ng/mL, between 20 and 29, and over 30 ng/mL, respectively.

Unsuccessful Electrical Cardioversion

AF detection in a 12-lead ECG following right after cardioversion or within a 6-month follow-up; or (2) ECG Holter monitoring of AF lasting more than thirty seconds at the 6-month follow-up after electrical cardioversion.

Laboratory Tests

Serum 25-hydroxyvitamin D levels were measured with a radioimmunoassay technique utilizing the Architect i2000 (Abbott Laboratories). The serum parathyroid hormone (PTH) concentration was

calculated with an immunoassay method (Siemens Immulite, Siemens Healthcare Diagnostics, Deerfield, IL, USA).

Echocardiography Acquisition

Skilled echocardiography fellows performed Transthoracic echocardiography using a Phillips Epiq 7c ultrasound system. Left ventricular ejection fraction (LVEF) was measured with the modified Simpson's biplane method[20]. Echocardiography was performed based on criteria of the American Society of Echocardiography and European Association of Echocardiography guidelines[21].

Statistical Analysis

Numeric variables were expressed as mean ± SD and categorical variables as number (%). The chi-square analysis, or Fisher exact test, assessed the significance of differences between categorical variables. Data analysis was conducted using SPSS software, version 26. A p-value less than 0.05 was considered statistically significant.

Results

In a study population of 190 patients, the mean age was 46.22±15.03 (range from 16 to 94 years). Males constituted 55.8% (n = 106) of the study population, with the remainder being females. Figure 1 illustrates the flowchart of the study design.

VDD, VDI, and VDS were observed in 77 (40.5%), 46 (24.2%), and 67 (35.3%) of the study population, respectively. The most prevalent symptom was palpitation, occurring in 27.36% of patients with VDD, 17.89% with VDI, and 23.1% with VDS. Fatigue and syncope were significantly more common in the VDD group than in other groups. Table 1 presents the symptoms of the study population in different groups along with the p-values.

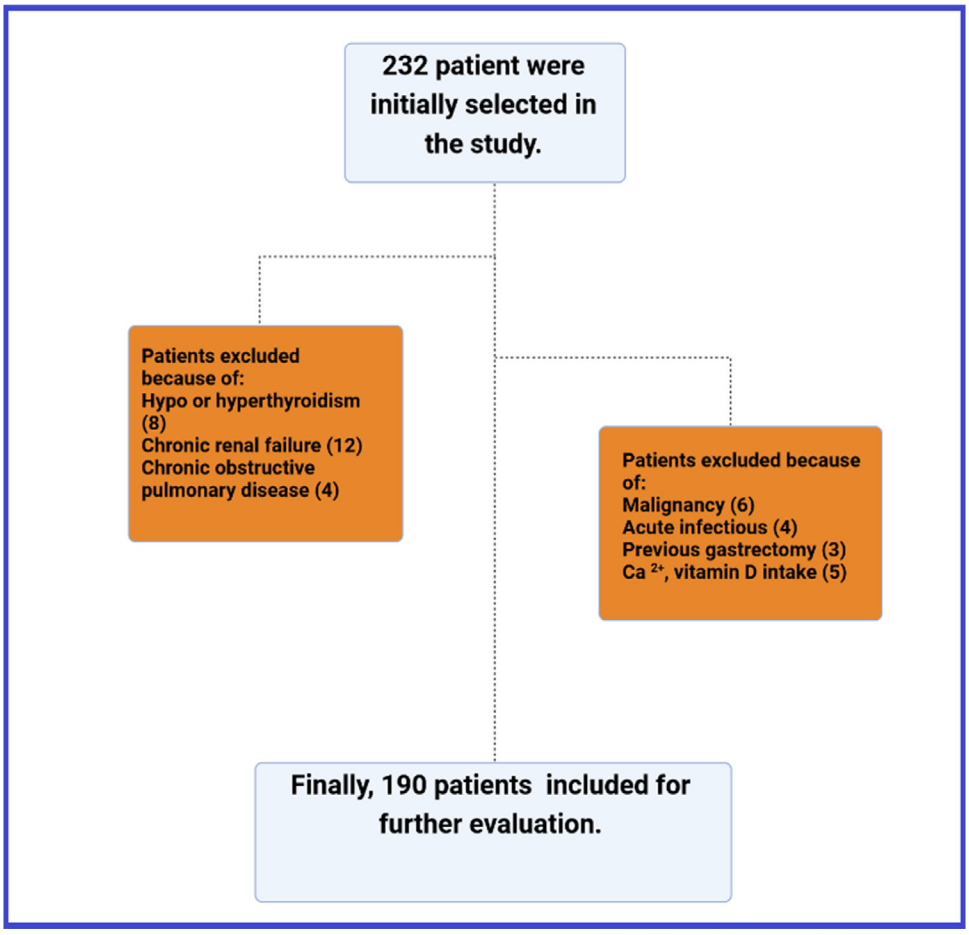

Figure 1. Flowchart of study design

Hypertension (p=0.03) and diabetes (p=0.01) were significantly more common in patients with VDD. Significant differences were observed in the prevalence of coronary artery disease among the VDD, VDI, and VDS groups (p=0.04); three-vessel disease was notably more common in the VDD group. Table 2 presents the distribution of comorbidities and risk factors among the three groups of patients.

Figure 2 depicts the mortality, successful electrical cardioversion, anticoagulant therapy, and valvular heart disease based on vitamin D levels in our study population. Mortality was more common in patients with VDD (n = 12, 6.31%) than in those with VDI (n = 4, 2.10%) and VDS (n = 2, 1.05%) groups (p = 0.03). Prior electrical cardioversion was observed in 12 (15.58%), 5 (10.86%), and 11 (16.41%) patients from the VDD, VDI, and VDS groups, respectively, without a significant statistical difference (p-value = 0.69). The success rate of electrical cardioversion was significantly higher in the VDS group than in the VDI and VDD groups (p = 0.03): 16.6%, 50%, and 81.8% in the VDD, VDI, and VDS groups, respectively. The need for anticoagulant therapy was significantly higher in the VDD group (p = 0.02). *= p-value < 0.05, SEC = successful electrical cardioversion

Table 1. Symptoms of the study population

Symptoms	VDD* n(%)	VDI* n(%)	VDS* n(%)	P-value
Palpitation	52(27.36%)	34(17.89%)	44(23.1%)	0.63
Dyspnea	17(8.94%)	18(9.4%)	20(10.52%)	0.12
Fatigue	15(7.89%)	13(6.84%)	3(1.57%)	0.02
Dizziness	5(2.63%)	4(2.10%)	3(1.57%)	0.66
Syncope	5(2.63%)	2(1.05%)	1(0.52%)	0.01
Anxiety	4(2.10%)	1(0.52%)	2(1.05%)	0.33
Chest pain	2(1.05%)	1(0.52%)	1(0.52%)	0.53

VDD* = Vitamin D deficiency, VDI*= Vitamin D insufficiency, VDS*= Vitamin D sufficiency

Chi square test was performed to evaluate the significant difference. P-value less than 0.05 was considered statistical significant.

Table 2. Comorbidities and risk factors distribution based on vitamin D

		VDD* n(%)	VDI* n(%)	VDS* n(%)	P-value
Hypertension		44(23.15%)	20(10.52%)	24(12.63%)	0.03*
Dyslipidemia		22(11.57%)	17(8.94%)	26(13.68%)	0.39
Diabetes		25(13.15%)	16(8.42%)	9(4.73%)	0.01*
Tobacco smoking		7(3.68%)	1(0.52%)	5(2.63%)	0.32
Opium		6(3.15%)	1(0.52%)	1(0.52%)	0.12
Coronary artery disease	**Normal**	52(27.36%)	35(18.42%)	61(32.10%)	0.04*
	Minimal coronary involvement	6(3.15%)	2(1.05%)	1(0.52%)	
	Two vessel disease	5(2.63%)	3(1.57%)	1(0.52%)	
	Three vessel disease	13(6.84%)	5(2.63%)	3(1.57%)	
CHA_2DS_2-VASc Score	**0**	8	9	13	0.03*
	1	35	13	38	
	2	15	12	11	
	≥3	19	10	4	

VDD* = Vitamin D deficiency, VDI*= Vitamin D insufficiency, VDS*= Vitamin D sufficiency

Chi square test was performed to evaluate the significant difference. P-value less than 0.05 was considered statistical significant.

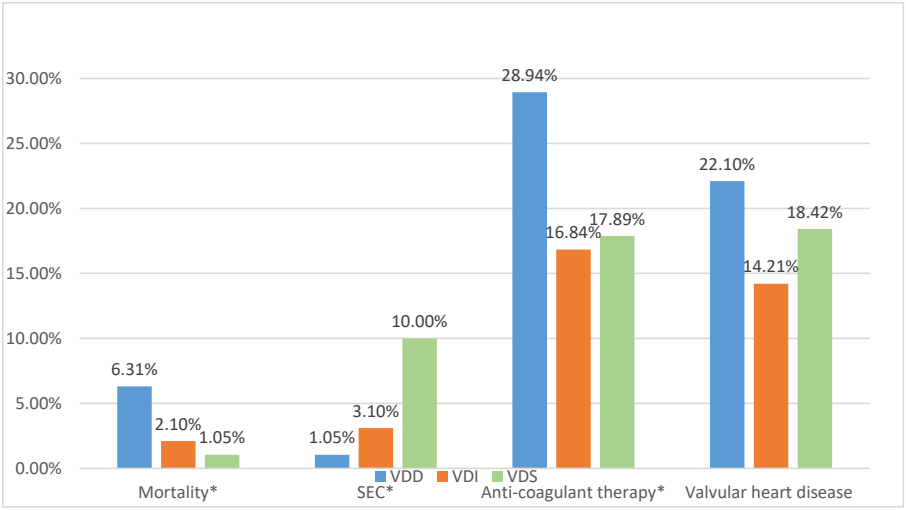

Figure 2. Mortality, successful electrical cardioversion, anticoagulant therapy, and valvular heart disease population based on vitamin D level

Discussion

VDD was observed in 40.5% of the study population. The authors noted that fatigue and syncope were significantly more prevalent in the VDD group than in other groups. Conditions such as diabetes, hypertension, three-vessel disease, and a CHA2DS2-VASc Score of ≥3 were more common in the VDD group. Furthermore, the authors found that mortality, unsuccessful electrical cardioversion, and the requirement for anticoagulant therapy were considerably higher in the VDD group.

VDD was observed in 40.5% of the study participants. This is consistent with the results of the prospective study by Qayyum et al., which analyzed vitamin D levels and found a prevalence of VDD (25-hydroxyvitamin D levels <20 ng/ml) of 42%[22]. In a prospective cohort study by Alonso et al., among 1866 patients who developed atrial fibrillation, 29% had a 25-hydroxyvitamin D level of less than 20 ng/ml. In the study by Ozcan et al., which compared 137 new-onset AF patients with 90 patients without AF, the rate of VDD (defined as 25-hydroxyvitamin D levels <20 ng/ml) in new-onset AF patients (VDD =67%) was significantly higher than the control group (VDD = 51%)[23]. The authors suggest that these differences among this study and other rates of VDD in the literature may be due to the limited type of AF of the study population, genetics, the time of vitamin D sampling, and other factors that interfere with the serum vitamin D level. In conclusion, the prevalence of VDD in AF patients appears to be between 30% and 40%.

In the present study, fatigue was significantly higher in the VDD group than in other groups. Beckmann et al. have reported that fatigue is associated with lower vitamin D levels[24]. Fatigue may present as a symptom of insufficient vitamin D levels, influencing a decrease in the optimal functioning of skeletal muscles through the modulation of vitamin D receptors[25]. These findings are in good agreement with the results of the authors' study.

Remarkably, syncope was more prevalent in the VDD group than in the VDI and VDS groups. Low vitamin D levels decrease serotonin production and release, decrease autonomic cardiac activity, and increase inflammation, leading to gastrointestinal dysfunction. All three mechanisms affect the brain, cardiac, and gastrointestinal autonomic systems[26]. VDD is associated with orthostatic hypotension in older adults[27]. In a study by Songül Usalp et al., VDD levels were significantly lower in patients with vasovagal syncope[28]. These results support the association of VDD with presenting symptoms, including fatigue and syncope. Patients with a diagnosis of AF who have the symptoms of fatigue and syncope should be evaluated for VDD.

Based on the results of this study, hypertension, diabetes, and three-vessel disease were considerably more common in the VDD group. Vitamin D deficiency plays a crucial role in hypertension through

the RAAS system[29]. The elimination of vitamin D receptors in recent animal studies has been linked to an increase in renin and angiotensin II levels and a decrease in endothelial nitric oxide (NO) synthase expression[30]. In alignment with the results of the authors' study, in a prospective cohort study of 3316 patients (1997–2000) in southwest Ludwigshafen, an increase in plasma renin and angiotensin II concentration was associated with decreased levels of 25-hydroxyvitamin D[31]. VDD is associated with hypertension through RAAS activation and decreased vasodilators such as NO.

In the present study, diabetes was more prevalent in the VDD group. In a systematic review and meta-analysis conducted by G. Pittas et al., a significant association was seen between low vitamin D levels and the prevalence of type 2 diabetes[32]. (OR=0.36, 95% CI [0.16, 0.80]) In a case-control study by Targher G et al. performed on 390 consecutive type 2 diabetic patients and 390 non-diabetic controls, greater carotid intimal medial thickness and the prevalence of carotid atherosclerotic plaques were more prevalent in diabetic patients[33]. In another study, VDD prevalence (39% vs. 25%) and vitamin D levels were significantly lower in diabetic versus non-diabetic participants ($p<0.008$)[34]. The results of our study are in good agreement with the studies mentioned above. These results suggest that VDD has a critical role in diabetes.

Atherosclerosis, a leading cause of vascular disease and a significant cause of mortality worldwide[35], is notably associated with VDD. VDD plays a protective role in atherosclerosis through various mechanisms, including inhibiting platelet and leukocyte aggregation, reducing the release of pro-inflammatory cytokines, modulating the immune response, decreasing endothelial oxidative stress, and releasing vasoconstrictor metabolites[36]. Based on the results of the authors' study, three-vessel disease was significantly more common in the VDD group. This is consistent with a retrospective single-center study of 100 patients undergoing coronary artery bypass grafting (CABG), where two or three-vessel disease was more prevalent in patients with VDD[37]. Similarly, in another single-center study of 239 patients undergoing coronary angiography, severe coronary artery disease was associated with lower vitamin D levels[38]. Interestingly, a decrease in VDR in the left anterior descending artery of a monkey's heart was associated with larger atherosclerotic plaques[39]. In conclusion, not only may VDD induce atherosclerosis, but lower levels of vitamin D are also associated with more severe coronary involvements.

Interestingly, successful electrical cardioversion was more prevalent in the VDS group than in the VDD and VDI groups. Few studies have explored the relationship between electrical cardioversion and vitamin D deficiency in patients with AF; however, some studies suggest a link between vitamin D deficiency and AF recurrence after electrical cardioversion[40,41].

The authors' results are consistent with the study by Fakhry et al. on 200 patients with persistent AF who needed electrical cardioversion, indicating that VDD was associated with AF cardioversion failure[41]. Among 51 patients who underwent CV for symptomatic AF, the patients in the AF recurrence group had a lower Vitamin D level compared with the non-recurrence group ($P=0.001$; 18 ng/ml vs. 26.3 ng/ml, respectively)[42]. Also, vitamin D deficiency has been associated with left atrial fibrosis and an increased risk of AF recurrence after ablation[43].

However, in a retrospective study analyzing 100 patients with atrial fibrillation who required cardioversion, there was no significant difference in cardioversion outcome based on VDD[44]. Notably, only 9% of the study population had VDD, and this low sample size may have influenced the results. In conclusion, the authors suggest that VDD may have an adverse effect on electrical cardioversion outcomes in patients with AF. Accordingly, correcting vitamin D levels is essential for AF patients, especially those with indications for electrical cardioversion.

To the authors' knowledge, this is the first report of the mortality of AF patients based on vitamin D levels. The authors found that the mortality rate of the VDD group was significantly higher than that of the other two groups. In a retrospective study of 13,331 adults older than 20 years old, it was concluded that the lowest quartile of vitamin D level (<17.8 ng/mL) is independently associated with all-cause mortality in the general population[45]. In a meta-analysis of prospective cohort studies, a nonlinear decrease in mortality risk was observed as circulating 25(OH) D increases within specific ranges (30–35 ng/ml). It is important to consider VDD as a risk factor for mortality in patients with AF[46]. Therefore, it is recommended that physicians monitor and correct

vitamin D levels in patients with AF.

According to the authors' study, AF patients with VDD significantly required more anticoagulant therapy than other groups. In a study performed on 75 patients with stable coronary artery disease, the mean platelet volume was significantly higher in patients with vitamin D levels < 10 ng/mL[47]. Activated vitamin D upregulates antithrombotic factor (AT) and thrombomodulin gene expression and downregulates thrombogenic factor (TF) gene expression in monocyte cells[48]. Vitamin D is also considered one of the antioxidant agents[49]. In the study by Takamasa Ishii et al., genetically induced oxidative stress in mice caused thrombocytosis[50]. It's noteworthy that vitamin D deficiency is a risk factor for stroke[51]. Interestingly, a CHA2DS2-VASc Score of ≥3 was more prevalent in the VDD group than in other groups. This finding may be due to the association between VDD and diabetes, hypertension, and heart failure[52]. Therefore, correcting vitamin D levels in AF patients at risk of thromboembolic events[53] seems to be an important therapeutic option for physicians managing AF patients.

The authors acknowledge that their research may have limitations. Vitamin D levels can fluctuate depending on the time of evaluation, which could potentially impact the study results. To mitigate this limitation, the authors assessed vitamin D levels from the onset of winter until the end of March. Although this was the first study to evaluate mortality in atrial fibrillation patients with VDD, it is crucial to interpret the findings cautiously, as other factors may influence mortality in these patients.

Conclusion

Indeed, VDD is a significant concern in patients with atrial fibrillation (AF). Symptoms such as fatigue and syncope were notably more prevalent in AF patients with VDD, underscoring the importance of monitoring vitamin D levels. Notably, VDD may not only induce atherosclerosis, but lower levels of vitamin D are also associated with more severe coronary involvements. It's crucial to consider VDD as a risk factor for mortality in patients with AF. Therefore, it's recommended that physicians monitor and correct vitamin D levels in patients with AF. While epidemiological studies have often, but not consistently, indicated that vitamin D deficiency is a risk factor for stroke, correcting vitamin D levels in AF patients at risk of thromboembolic events appears to be a vital therapeutic option for physicians managing AF patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

The authors would like to declare that they did not receive any financial support for this study.

Author's Contributions

All individuals who satisfy the established criteria for authorship are acknowledged as authors, and each author affirms their substantial involvement in the research process, thereby considering a public responsibility for the content. This involvement includes contributions to the conceptualization, design, analysis, writing, and revision of the manuscript.

References

1. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nat Rev Cardiol. 2014 Nov;11(11):639-54. https://doi.org/10.1038/nrcardio.2014.118
2. Lane DA, Skjøth F, Lip GYH, Larsen TB, Kotecha D. Temporal Trends in Incidence, Prevalence, and Mortality of Atrial Fibrillation in Primary Care. J Am Heart Assoc. 2017 Apr 28;6(5):e005155. https://doi.org/10.1161/JAHA.116.005155
3. Björck S, Palaszewski B, Friberg L, Bergfeldt L. Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study. Stroke. 2013 Nov;44(11):3103-8. https://doi.org/10.1161/STROKEAHA.113.002329
4. Krijthe BP, Kunst A, Benjamin EJ, Lip GYH, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J. 2013 Sep;34(35):2746-51. https://doi.org/10.1093/eurheartj/eht280
5. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable Risk Factors and Atrial Fibrillation. Circulation 2017;136(6):583-96. https://doi.org/10.1161/CIRCULATIONAHA.116.023163
6. Guta AC, Badano LP, Tomaselli M, Mihalcea D,

Bartos D, Parati G, et al. The Pathophysiological Link between Right Atrial Remodeling and Functional Tricuspid Regurgitation in Patients with Atrial Fibrillation: A Three-Dimensional Echocardiography Study. J Am Soc Echocardiogr. 2021 Jun;34(6):585-594.e1. https://doi.org/10.1016/j.echo.2021.01.004

7. Kassi E, Adamopoulos C, Basdra EK, Papavassiliou AG. Role of vitamin D in atherosclerosis. Circulation. 2013 Dec 3;128(23):2517-31. https://doi.org/10.1161/CIRCULATIONAHA.113.002654
8. Beveridge L, Witham M. Vitamin D and the cardiovascular system. Osteoporos Int 2013;24:2167-80. https://doi.org/10.1007/s00198-013-2281-1
9. Turin A, Bax JJ, Doukas D, Joyce C, Lopez JJ, Mathew V, et al. Interactions Among Vitamin D, Atrial Fibrillation, and the Renin-Angiotensin-Aldosterone System. Am J Cardiol 2018;122(5):780-4. https://doi.org/10.1016/j.amjcard.2018.05.013
10. Hu Y-F, Chen Y-J, Lin Y-J, Chen S-A. Inflammation and the pathogenesis of atrial fibrillation. Nat Rev Cardiol 2015;12(4):230-43. https://doi.org/10.1038/nrcardio.2015.2
11. Heidarali M, Bakhshandeh H, Golpira R, Fazelifar A, Alizadeh-Diz A, Emkanjoo Z, et al. A prospective survey of atrial fibrillation management in Iran: Baseline results of the Iranian Registry of Atrial Fibrillation (IRAF). Int J Clin Pract. 2021;75(8):e14313. https://doi.org/10.1111/ijcp.14313
12. Flack JM, Adekola B. Blood pressure and the new ACC/AHA hypertension guidelines. Trends Cardiovasc Med. 2020;30(3):160-4. https://doi.org/10.1016/j.tcm.2019.05.003
13. Halawani AFM, Alahmari ZS, Asiri DA, Albraheem AA, Alsubaie AMA, Alqurashi AG, et al. Diagnosis and Management of Dyslipidemia. Arch Pharm Pract 2019;10(4):67-70.
14. Chamberlain JJ, Rhinehart AS, Shaefer CF, Neuman A. Diagnosis and Management of Diabetes: Synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes. Ann Intern Med 2016;164(8):542-52. https://doi.org/10.7326/M15-3016
15. Cesar L, Ferreira J, Armaganijan D, Gowdak L, Mansur A, Bodanese LC, et al. Guideline for stable coronary artery disease. Arq Bras Cardiol 2014;103:01-59. https://doi.org/10.5935/abc.2014S004
16. Weintraub WS, King III SB, Douglas Jr JS, Kosinski AS. Percutaneous transluminal coronary angioplasty as a first revascularization procedure in single-, double-and triple-vessel coronary artery disease. J Am Coll Cardiol 1995;26(1):142-51. https://doi.org/10.1016/0735-1097(95)00136-N
17. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137(2):263-72. https://doi.org/10.1378/chest.09-1584
18. Dilaveris PE, Kennedy HL. Silent atrial fibrillation: epidemiology, diagnosis, and clinical impact. Clin Cardiol 2017;40(6):413-8. https://doi.org/10.1002/clc.22667
19. Group CW. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2013;3(1):1-150.
20. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015; 16(3):233-70. https://doi.org/10.1093/ehjci/jev014
21. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2019;32(1):1-64. https://doi.org/10.1016/j.echo.2018.06.004
22. Qayyum F, Landex NL, Agner BR, Rasmussen M, Jøns C, Dixen U. Vitamin D deficiency is unrelated to type of atrial fibrillation and its complications. Dan Med J 2012;59(9):A4505.
23. Ozcan OU, Gurlek A, Gursoy E, Gerede DM, Erol C. Relation of vitamin D deficiency and new-onset atrial fibrillation among hypertensive patients. J Am Soc Hypertens 2015;9(4):307-12. https://doi.org/10.1016/j.jash.2015.01.009
24. Beckmann Y, Türe S, Duman SU. Vitamin D deficiency and its association with fatigue and quality of life in multiple sclerosis patients. EPMA J 2020;11:65-72. https://doi.org/10.1007/s13167-019-00191-0
25. Roy S, Sherman A, Monari-Sparks MJ, Schweiker O, Hunter K. Correction of Low Vitamin D Improves Fatigue: Effect of Correction of Low Vitamin D in Fatigue Study (EViDiF Study). N Am J Med Sci 2014;6(8):396-402. https://doi.org/10.4103/1947-2714.139291
26. Wadhwania R. Is Vitamin D Deficiency Implicated in Autonomic Dysfunction? J Pediatr Neurosci 2017;12(2):119-23. https://doi.org/10.4103/jpn.JPN_1_17
27. Gilani A, Ramsay SE, Welsh P, Papacosta O, Lennon LT, Whincup PH, et al. Vitamin D deficiency is

associated with orthostatic hypotension in older men: a cross-sectional analysis from the British Regional Heart Study. Age Ageing 2020;50(1):198-204. https://doi.org/10.1093/ageing/afaa146
28. Usalp S, Kemal H, Yüksek Ü, Yaman B, Günsel A, Edebal O, et al. Is there any link between vitamin D deficiency and vasovagal syncope? J Arrhythm 2020;36(2):371-6. https://doi.org/10.1002/joa3.12309
29. Han L, Xu X-J, Zhang J-S, Liu H-M. Association between Vitamin D Deficiency and Levels of Renin and Angiotensin in Essential Hypertension. Int J Clin Pract 2022: 8975396. https://doi.org/10.1155/2022/8975396
30. Ni W, Watts SW, Ng M, Chen S, Glenn DJ, Gardner DG. Elimination of vitamin D receptor in vascular endothelial cells alters vascular function. Hypertension 2014;64(6):1290-8. https://doi.org/10.1161/HYPERTENSIONAHA.114.03971
31. Tomaschitz A, Pilz S, Ritz E, Grammer T, Drechsler C, Boehm BO, et al. Independent association between 1, 25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin-angiotensin system: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Clin Chim Acta 2010;411(17-18):1354-60. https://doi.org/10.1016/j.cca.2010.05.037
32. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The Role of Vitamin D and Calcium in Type 2 Diabetes. A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab 2007;92(6):2017-29. https://doi.org/10.1210/jc.2007-0298
33. Targher G, Bertolini L, Padovani R, Zenari L, Scala L, Cigolini M, et al. Serum 25-hydroxyvitamin D3 concentrations and carotid artery intima-media thickness among type 2 diabetic patients. Clin Endocrinol 2006;65(5):593-7. https://doi.org/10.1111/j.1365-2265.2006.02633.x
34. Isaia G, Giorgino R, Adami S. High prevalence of hypovitaminosis D in female type 2 diabetic population. Diabetes Care 2001;24(8):1496. https://doi.org/10.2337/diacare.24.8.1496
35. Herrington W, Lacey B, Sherliker P, Armitage J, Lewington S. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. Circ Res 2016;118(4):535-46. https://doi.org/10.1161/CIRCRESAHA.115.307611
36. Menezes AR, Lamb MC, Lavie CJ, DiNicolantonio JJ. Vitamin D and atherosclerosis. Curr Opin Cardiol 2014;29(6):571-7. https://doi.org/10.1097/HCO.0000000000000108
37. Syal SK. Vitamin D deficiency, coronary artery disease, and endothelial dysfunction: observations from a coronary angiographic study in Indian patients. J Invasive Cardiol 2012;24(8): (8):385-9.
38. Akin F, Ayça B, Köse N, Duran M, Sarı M, Uysal OK, et al. Serum vitamin D levels are independently associated with severity of coronary artery disease. J Investig Med 2012;60(6):869-73. https://doi.org/10.2310/JIM.0b013e31825457cb
39. Schnatz PF, Nudy M, O'Sullivan DM, Jiang X, Cline JM, Kaplan JR, et al. The quantification of vitamin D receptors in coronary arteries and their association with atherosclerosis. Maturitas 2012;73(2):143-7. https://doi.org/10.1016/j.maturitas.2012.03.014
40. Yaman B, Cerit L, Günsel HK, Cerit Z, Usalp S, Yüksek Ü, et al. Is there any link between vitamin d and recurrence of atrial fibrillation after cardioversion? Braz J Cardiovasc Surg 2020;35:191-7. https://doi.org/10.21470/1678-9741-2019-0166
41. Effat Fakhry E, Tawfik Ibrahim M. Relationship between vitamin D deficiency and success of cardioversion in patients with atrial fibrillation. Herzschrittmacherther Elektrophysiol 2022;33(2):209-16. https://doi.org/10.1007/s00399-022-00846-y
42. Yaman B, Cerit L, Günsel HK, Cerit Z, Usalp S, Yüksek Ü, et al. Is there any Link Between Vitamin D and Recurrence of Atrial Fibrillation after Cardioversion? Braz J Cardiovasc Surg 2020;35(2):191-7. https://doi.org/10.21470/1678-9741-2019-0166
43. Canpolat U, Aytemir K, Hazirolan T, Özer N, Oto A. Relationship between vitamin D level and left atrial fibrosis in patients with lone paroxysmal atrial fibrillation undergoing cryoballoon-based catheter ablation. J Cardiol 2017;69(1):16-23. https://doi.org/10.1016/j.jjcc.2016.06.012
44. Hussain A, Al Anazi F, Alanazi A, Alshahrani A, Alharbi N, Aleshaiwy T, et al. The relation between atrial fibrillation cardioversion success rate with Vitamin D Level in patients underwent elective cardioversion in King Abdulaziz Cardiac Center, King Abdulaziz Medical City for National Guards, Riyadh Saudi Arabia. Heart Views 2023;24(1):17-23. https://doi.org/10.4103/heartviews.heartviews_80_22
45. Melamed ML, Michos ED, Post W, Astor B. 25-Hydroxyvitamin D Levels and the Risk of Mortality in the General Population. Arch Intern Med 2008;168(15):1629-37. https://doi.org/10.1001/archinte.168.15.1629
46. Zhang Z, Yang Y, Ng CY, Wang D, Wang J, Li G, et al. Meta-analysis of Vitamin D Deficiency and Risk of Atrial Fibrillation. Clin Cardiol 2016;39(9):537-43. https://doi.org/10.1002/clc.22563
47. Korzonek-Szlacheta I, Hudzik B, Nowak J, Szkodzinski J, Nowak J, Gąsior M, et al. Mean platelet volume is associated with serum 25-hydroxyvitamin

D concentrations in patients with stable coronary artery disease. Heart Vessels 2018;33(11):1275-81. https://doi.org/10.1007/s00380-018-1182-9

48. Aihara K-i, Azuma H, Akaike M, Ikeda Y, Yamashita M, Sudo T, et al. Disruption of nuclear vitamin D receptor gene causes enhanced thrombogenicity in mice. J Biol Chem 2004;279(34):35798-802. https://doi.org/10.1074/jbc.M404865200
49. Peery SL, Nemere I. Contributions of pro-oxidant and anti-oxidant conditions to the actions of 24, 25-dihydroxyvitamin D3 and 1, 25-dihydroxyvitamin D3 on phosphate uptake in intestinal cells. J Cell Biochem 2007;101(5):1176-84. https://doi.org/10.1002/jcb.21238
50. Ishii T, Miyazawa M, Takanashi Y, Tanigawa M, Yasuda K, Onouchi H, et al. Genetically induced oxidative stress in mice causes thrombocytosis, splenomegaly and placental angiodysplasia that leads to recurrent abortion. Redox Biol 2014;2:679-85. https://doi.org/10.1016/j.redox.2014.05.001
51. Poole KE, Loveridge N, Barker PJ, Halsall DJ, Rose C, Reeve J, et al. Reduced vitamin D in acute stroke. Stroke 2006;37(1):243-5. https://doi.org/10.1161/01.STR.0000195184.24297.c1
52. Pilz S, März W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. J Clin Endocrinol Metab 2008;93(10):3927-35. https://doi.org/10.1210/jc.2008-0784
53. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial Fibrillation. Circ Res 2017;120(9):1501-17. https://doi.org/10.1161/CIRCRESAHA.117.309732

How to cite this article: Askarinejad A, Bakhshandeh H, Heidarali M, Adimi S, Ghaemmaghami Z, Haghjoo M. **Vitamin D deficiency and atrial fibrillation: A cross sectional single center study.** ARYA Atheroscler 2024; 20(1): 31-40.